(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 August 2004 (19.08.2004)

PCT

(10) International Publication Number
WO 2004/069229 A1

(51) International Patent Classification[7]: A61K 9/24, 31/155, A61P 3/10

(21) International Application Number:
PCT/IN2003/000313

(22) International Filing Date:
17 September 2003 (17.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
152/MUM/2003 5 February 2003 (05.02.2003) IN

(71) Applicant *(for all designated States except US)*: **IPCA LABORATORIES LIMITED** [IN/IN]; 48, Kandivli Industrial Estate, Kandivli Industrial Estate, Kandivli (West), Mumbai 400 067, Maharashtra (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **THEMBALATH, Ramachandran** [IN/IN]; 6/35, Prakash Co. Housing Society, Relief Road, Santacruz (West), Mumbai 400 054, Maharashtra (IN). **BANSAL, Yatish, Kumar** [IN/IN]; Flat No.3, Siras Villa, Plot No.40, Sai Baba Park, Evershine Nagar, Malad (West), Mumbai 400 064, Maharashtra (IN). **TAWDE, Vaishali, Manish B-2, 14th Forjett Terrace** [IN/IN]; Forjett Hill Road, Opp. Bhatya Hospital, Grant Road, Mumbai 400 036, Maharashtra (IN). **JADHAV, Vivek, Kamlakar** [IN/IN]; Flat No. 2, R. R. Sabji Co-op. Society, 10, Ram Baug, Andheri (West), Mumbai 400 058, Maharashtra (IN).

(74) Agent: NAIR, Gopakumar, G.; Gopakumar Nair Associates, Nair Baug, Akurli Road, Kandivli (East), Mumbai 400 101 (IN).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DUAL RELEASE ANTI-DIABETIC DRUGS AND PROCESS OF PRODUCTION THEREOF

(57) Abstract: The present invention relates to a process for dual release combination of pharmaceutical ingredients, more particularly, antidiabetic drugs, comprising extended release of biguanide and immediate release of thiazolinedione in a multilayer formulation.

WO 2004/069229 A1

DUAL RELEASE ANTI-DIABETIC DRUGS AND PROCESS OF PRODUCTION THEREOF

Related Application

This application claims priority from India National patent application serial No. 152/MUM/2003, filed 5th February 03.

Field of the Invention

The invention relates to the field of medicine and pharmacology. More specifically, the invention relates to a pharmaceutical composition comprising at least two different pharmaceutically active ingredients, the release profile of a first active ingredient being different from the release profile of a second active ingredient. The pharmaceutical composition of the invention is particularly indicated in the treatment of diabetes.

Background and Prior Art

It is well known in the pharmaceutical field to provide delivery systems for the controlled release of pharmaceutically active ingredients. Such systems allow for the delivery after administration of a pharmaceutical dose sustained over a period of time. As well as direct pharmacological benefits of such sustained release, it is generally thought that patient compliance with the treatment protocol is also improved as a result

of a diminished need for repetitive administration. WO-A-02/28383 for example discloses a delivery system for chiral pharmaceutical agents.

Diabetes mellitus is a group of disorders of carbohydrate metabolism in which the action of insulin is diminished or absent through altered secretion, decreased insulin activity or a combination of both factors. Of the several known types of diabetes mellitus, the two major types are type I (insulin-dependent diabetes mellitus; IDDM) and type II (non-insulin-dependent diabetes mellitus; NIDDM).

Type II diabetes mellitus is a common disease increasingly affecting people worldwide. While type II diabetes affects less than 10% of the population in developed countries, the prevalence of the disease is growing faster among the Asian population especially Asian immigrants. Antidiabetic drugs have therefore become an area of immense interest and attention for the research community throughout the world.

First line therapy in both type I and type II diabetes involves dietary control and, especially in the case of type II diabetes, increased exercise routine. If patients with type II diabetes have not achieved suitable control within about three months after dietary modification and increased physical activity, then oral hypoglycemic drugs may be indicated. The two major classes of such drugs are thiazolinediones and biguanides. Thiazolinediones act mainly by enhancing insulin sensitivity in peripheral tissues. Biguanides act chiefly by decreasing hepatic gluconeogeneis and increasing peripheral utilization of glucose.

Metformin (N, N – dimethyl imidocarbonimidic diamide) is a typical biguanide and is an active ingredient used in oral hypoglycemic drugs for the treatment of type II diabetes mellitus in humans and other mammals. It is typically administered in the form of a pharmaceutically acceptable salt, usually a hydrochloride salt. Metformin is not chemically or pharmacologically related to any other class of hypoglycemic agents. Unless otherwise indicated, this specification will use "metformin" to mean metformin and pharmaceutically acceptable salts thereof. Metformin is often indicated for patients who are not effectively treated with a thiazolinedione drug independently. Metformin hydrochloride is a white to off-white crystalline compound having the molecular formula $C_4H_{11}N_5.HCl$ (molecular wt. 165.63) and is freely soluble in water and practically insoluble in acetone, ether and chloroform. Oral doses of metformin are generally recommended in the range of 500 to 2500 mg a day and a single dose may vary from 500 to 850 mg. Metformin can exert its hypoglycemic effect even in the absence of insulin, particularly in patients who are not effectively treated with sulfonylureas.

Pioglitazone belongs to the class of thiazolinediones which act primarily by decreasing insulin resistance. They partially mimic certain actions of insulin on carbohydrate and lipid metabolism in type II diabetes mellitus and other conditions of insulin resistance. Pioglitazone, rosiglitazone and troglitazone are the most commonly used thiazolinediones (glitazones).

Metformin is not chemically related to thiazolinediones, but it is routinely used in combination with a thiazolinedione, such as troglitazone, pioglitazone, etc., and shows

synergistic properties in some cases. Other biguanides such as phenformin and buformin can also be used in combination with metformin.

US Patent 6,011,049 discloses a combination therapy for metformin along with a thiazolinedione and establishes unexpected biological benefits of these combinations in the context of conventional drug formulation.

A controlled release once-a-day single drug formulation of sulfonylurea is disclosed in US Patent 6,056,977.

US Patent 6,372,255 describes a tablet for instant and prolonged release of one or more active substances, by means of concentric superposed layers using a non-biodegradable, inert porous polymetric matrix comprising ethyl acrylate and methyl methacrylate copolymers.

US Patent 6,403,121 and US Patent 6,451,342 describe a controlled release formulation of pioglitazone with metformin and troglitazone with metformin respectively. These drugs are subjected to controlled release using silicates and alginates (poly saccharides) as modulating release agents.

US Patent 6,475,521 claims a biphasic controlled release delivery system for high solubility pharmaceuticals including metformin. In this case also, the emphasis is on controlled release and extended release using biphasic layers of a single active ingredient.

Pioglitazone hydrochloride being relatively non-polar, has relatively low solubility and therefore its absorption is dependent on its dissolution rate in the contents of the gastro-intenstinal tract, in contrast to metformin which is highly soluble. Metformin is usually used in the form of metformin hydrochloride. Metformin hydrochloride has a very high water solubility (>300mg/ml at 25°C). This high solubility of metformin leads to difficulty in providing a slow release rate from a formulation. Controlling the initial burst of metformin in a formulation containing more than one active ingredients is a problem often encountered. This problem is further complicated due to the high dosage of 500mg and above which is required for treatment.

US Patent 6,031,004 describes a method for the treatment of diabetes employing metformin hydrochloride and other salts by themselves or in combination with another anti-diabetic agent (e.g. a hypoglycemic agent such as glyburide, glipizide, pioglitazone, acarbose, miglitol, troglitazone or insulin). The dosage is disclosed as an oral tablet form. Metformin salts of dibasic acids that are equivalent to metformin hydrochloride are also described.

US Patent 6,475,521 discloses a biphasic controlled release system for high solubility pharmaceuticals. A metformin hydrochloride salt or a salt of metformin with a dibasic acid is used in combination with another hypoglycemic agent, for example a thiazolinedione such as glyburide, pioglitazone, glipizide, gliclazide or chlorpropamide, for the treatment of diabetes. The combination of active agents with a suitable excipient

(a hydrophilic and/or hydrophobic polymer) is said to provide controlled release and an extended biphasic release delivery system.

US Patent 6,524,618 describes an extended-release matrix formulation capable of being directly compressed into tablets comprising metformin hydrochloride blended with specific excipients in the form of a free flowing powder. Metformin hydrochloride is also used in combination with another anti-diabetic agents selected from the group consisting of thiazolinediones (eg. pioglitazone, glipyride, glipizide, glyburide, and gliciazide), α-glucosidaze inhibitors and glitazones as well as combinations of two or more of the foregoing anti-diabetic agents.

WO-A-02094285 describes orally administered galenic preparations (such as tablets, capsules, powders and the like), which consist of biguanide, preferably metformin and at least one other hypoglycemic active agent (glibenclamide, pioglitazone hydrochloride, rosiglitazone maleate, nateglinide, glipizide, pioglitazone). This capsule-shaped tablet consists of a core based on metformin further coated with a film that enables prolonged release *in vivo* of metformin. Optionally the capsule may be coated with the said at least one other hypoglycemic active agent and may allow for the prolonged release of the agent.

Although single dose combination preparations with active agents are known in the prior art for the treatment of diabetes, the combination agents are generally released simultaneously either at administration or over a period of time. Such preparations, although convenient, may not be as effective for treatment as two separately

administered doses of individual active agents and this may be for a number of reasons. For example, one agent may require a slower release profile in relation to another agent in order to be effective. It may also be the case that both agents have similar modes of pharmacological action and the action of one or both may therefore be inhibited by simultaneous release with the other because both are competing for the same or similar receptor.

Summary of the Invention

It is an object of the invention to provide an improved pharmaceutical composition, in particular for the treatment of diabetes. It is a further object of the invention to overcome or ameliorate one of more of the problems associated with the prior art pharmaceutical preparations. It is also an object of the present invention to provide a pharmaceutical preparation comprising two or more active ingredients, at least two of the active ingredients having different release profiles. Furthermore, it is also an object of the present invention to provide a pharmaceutical preparation comprising two or more active ingredients that act synergistically against a disease or condition. It is also an object of the invention to counteract the contrasting solubility of two active ingredients in a combination drug, and the normal release pattern arising out of the said solubility characteristics, by providing a synergistic formulation wherein the relatively insoluble active ingredient is released immediately and the relatively soluble active ingredient is released in an extended manner.

According to the present invention there is provided a pharmaceutical composition comprising a matrix material having first pharmaceutically active agent dispersed therein, the dispersion of the first agent within the matrix material being effective to delay the release profile on administration of the pharmaceutical composition with respect to the release profile of a second pharmaceutically active agent provided in the composition outside of the matrix material.

Detailed Description

The first pharmaceutically active agent and the second pharmaceutically active agent may, in one preferred composition according to the invention, be independently indicated in the treatment of diabetes.

Preferably, the first pharmaceutically active agent and the second pharmaceutically active agent are selected from respectively different classes of chemical compound.

The first and second active agents in the composition may be selected to exhibit a synergistic effect for treatment of a disease or a condition, such as diabetes.

In one preferred composition according to the invention, the first pharmaceutically active agent is a biguanide compound, preferably metformin.

In another preferred composition according to the invention, the second pharmaceutically active agent is a thiazolinedione compound, preferably pioglitazone.

The matrix material is preferably a polymeric material or mixture of polymeric materials and is preferably insoluble or only sparingly soluble in water. Preferably the matrix material has the capacity to absorb water from its surrounding environment and to swell on such absorption. Preferred polymeric materials include carbomers, such as carbomer 971, cellulosic polymers and alkyl cellulosic polymers such as methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxy propyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl methyl cellulose phthalate and mixtures of two or more thereof. Hydroxypropyl methyl cellulose is especially preferred, preferably with a viscosity in the range of 15000 – 100000 cps. Combinations of carbomers with cellulosic polymers are also particularly suitable as the matrix material.

Preferably, the matrix material is biodegradable.

The polymer of the matrix material may account for 15-25% or 15-20% of the total mass of the pharmaceutical composition

Preferably, the first pharmaceutically active agent is dispersed substantially homogenously throughout the matrix material.

On administration of the pharmaceutical composition of the invention, it is preferred that the release profile of the second pharmaceutically active agent be such that release of the second agent begins only a short time, for example in less than about 30 minutes, preferably less than about 15 minutes and most preferably less than about 5 minutes after

administration. Release of the second agent may begin substantially immediately after administration. Release of the first pharmaceutically active agent is delayed relative to the second agent, and may also be extended to take place over a longer timescale with respect to the second agent.

In one preferred composition according to the invention, the second pharmaceutically active agent is less soluble in water, preferably substantially less soluble in water, than the first pharmaceutically active agent. The second pharmaceutically active agent may be insoluble, or only sparingly soluble, in water.

The second active agent, thiazolinedione for example, may conveniently be provided in combination with a solubilising agent to provide a predetermined substantially immediate release on administration of the composition. Sodium lauryl sulphate is one preferred solubilising agent, which may suitably be present in an amount of from 0.2-2% of the total mass of the composition.

The second active agent may be therefore provided in combination with an effective amount of one or more immediate release excipients selected, for example, from one or more of: sodium starch glycolate, sodium lauryl sulphate, croscarmellose sodium and betacyclodextrin.

The pharmaceutical composition of the invention is suitably provided in a tablet form for oral administration and is preferably provided as a layered tablet, with a first layer comprising the matrix material and the first pharmaceutically active agent (optionally in

combination with other excipients, colourants, binders, diluents, disintegrants, fillers, lubricants, glidants, taste-masking agents and the like) and a second layer comprising the second pharmaceutically active agent (optionally in combination with other exipients, colourants, diluents, disintegrants, binders, fillers, lubricants, glidants, taste-masking agents and the like).

The first active agent may suitably be present in the first layer in an amount ranging from 500 mg to 850 mg. The second active agent may suitably be present in the second layer in an amount ranging from 15 mg to 45 mg.

When a binding agent is present in the composition, preferred binding agents (for combination with the first active agent) include polyvinylpyrrolidone, starch or mixtures thereof. When present, polyvinylpyrrolidone preferably has a grade varying from 10 - 120. The percentage of binding agent, when present, is preferably from 1-10% of the total mass of the composition. When polyvinylpyrrolidone is used as the binding agent it may be of K value 90 or with grade 90.

When a diluent is present in the composition, preferred diluents (provided in combination with the second active agent) include micro crystalline cellulose, starch and lactose. Such diluents, when used, may suitably be present in an amount of from 5-10% of the total mass of the composition. Also, preferred diluents (provided in combination with first or second active agents) include microcrystalline cellulose, dicalcium phosphate or mixtures thereof. Such diluents may suitably be present in an amount of from 10 – 20 % of the total mass of the composition.

When a disintegrant is present in the composition, preferred disintegrants (provided in combination with the second active agent) include sodium starch glycolate and croscarmellose sodium. Such disintegrants may suitably be present in an amount of from 0.2-2% of the total mass of the composition.

When a lubricant is present in the composition, a preferred lubricant (for combination with the first active agent) is magnesium stearate. Such lubricants may suitably be present in an amount of from 0.01-0.02% of the total mass of the preparation.

When a glidant is present in the composition, a preferred glidant (provided in combination with first or second active agents) is colloidal silicon dioxide. Such glidants may suitably be present in an amount of from 1-2% of the total mass of the composition.

Accordingly, the invention provides a pharmaceutical preparation in tablet form comprising two or more active ingredients with pre-determined release profiles, at least one active ingredient having a release profile that differs substantially from the release profile of another of the other active ingredient.

Preferred pharmaceutical compositions of the invention will: provide immediate release of thiazolinedione by using a solubilizing agent in an effective manner in a first layer; use a combination of two specific hydroxypropyl methyl cellulose and/or carbomer polymers in a second layer to aid effective release of the drug over a specific period of time independent of pH affects; provide a two drug combination therapy having a

synergistic effect over control of blood glucose in diabetic patients; allow reduced frequency of drug dosing and hence improve patient compliance; maintain a steady drug concentration in the blood circulation with the help of a sustained release layer; and minimize incidence and severity of adverse side effects.

The present invention therefore relates to a pharmaceutical composition adapted for dual release at different rates of combined pharmaceutical active agents, for example agents having anti-diabetic activity, in which at least one of the active ingredients is, preferably homogenously, dispersed throughout a rate controlling polymer matrix, release of the at least one active ingredient being controlled by diffusion through the matrix, and in which at least one other active agent is provided in the composition in a form available for rapid release *in vivo*.

In accordance with present invention there is provided a pharmaceutical preparation in tablet form comprising two or more active ingredients with pre-determined release profiles, at least one active ingredient having a release profile that differs substantially from the release profile of at least one other active ingredient. Each active ingredient may be disposed in a discrete layer within the tablet. Additionally, the at least two release profiles may comprise an extended release profile and an immediate release profile. The present invention also relates to the pharmaceutical preparation of a bi-layer tablet suitable for oral administration. Each tablet is preferably made up of immediate release compartment and extended release compartment. The immediate release compartment may comprise a compressed blend of an active agent and one or more polymers with some super disintegrant and solubilisers. The extended release

compartment may comprise biodegradable/non-biodegradable or hydrophilic /hydrophobic polymers which have swelling properties within which an active ingredient is suitably blended and this allows prolonged release of active substance within the second layer.

When the extended release compartment is in contact with the immediate release compartment it provides a dose sufficient to exceed the metabolic capacity of the body and maintains the therapeutic levels.

The invention is not limited as to the nature of the active ingredients. Each layer may contain a different active ingredient. The first layer may contain up to 50-80% of the active substance of the total weight of the first layer. The second layer may contain up to 3-10% by weight of the active ingredient.

Drug efficacy generally depends on the ability of the drug to reach its target in sufficient quantities, to maintain desired therapeutic levels for a fixed (desired) time period.

Metformin and pioglitazone are two active ingredients for anti-diabetic drugs that are used to treat diabetic patients (human beings).

The use of the core formulation involving both the active ingredients is advantageous to patients and physicians because both medicaments are synergistic to each other in the body when used in the management of blood glucose control. I.e.: diabetes.

In one pharmaceutical composition of the invention, the matrix material polymer is associated to the biguanide by forming a core within the preparation to provide a predetermined delay in the time period of the release of the biguanide.

The compartmentalized (two compartments or more) delivery of active ingredients in the intestinal tract is facilitated by the product formulation, taking into account the physical & physiological conditions in the human GI tract and also the travelling time of the pharmaceutical preparation through the intestinal tract.

In the dual compartment delivery, the immediate release ingredient releases within 45 minutes in acidic pH (stomach), and the extended release ingredient releases within 10 hrs at a different pH.

Orally administered drugs have to overcome several obstacles to reach their desired targets. Before orally administered drugs enter the general circulation of the human body they are absorbed into the capillaries and veins of the GI tract and are transported by the portal vein to the liver. The pH and enzymatic activities found in the GI tract fluids may inactivate the drug or cause the drug to dissolve poorly. Thus the amount of drugs in the blood stream is significantly lower than the amount administered. This metabolic elimination of the given dose results in bioavailability.

Formulations capable of immediate and sustained release are suitable for once daily administration.

Therefore, in accordance with the present invention, there is provided a multilayer formulation that provides dual release of two different pharmaceutically active agents in an effective manner in single dosage form. Furthermore, the present invention may provide immediate release of thiazolinedione by using a solubilizing agent in an effective manner in an upper layer. The use of a combination of two specific hydroxypropyl methyl cellulose polymers in the lower layer helps for the drug to release effectively over a specific period of time independent of pH affects. Preferably, the two drugs in the combination therapy are selected to have a synergetic effect over control of glucose in blood in diabetic patients. The combination therapy formulation may assist in the reduced frequency of drug dosing and hence improving patient compliance. The formulation preferably maintains a steady drug concentration in blood circulation with the help of sustained release layer and minimises incidence and severity of adverse side effects.

The multi-layer formulation is such that the upper layer comprises pioglitazone hydrochloride which is formulated by using solubilizing agent, disintegrating agent and wetting agent to make it effective for immediate release and the second layer which may or may not separate upper layer and lower layer which may or may not comprise metformin with a portion or all the amount of cellulose polymer depending upon the rate of release of the core preparation.

Accordingly, the present invention relates to a process for dual release combination of pharmaceutical active ingredients, more particularly, antidiabetic drugs, comprising

extended release of biguanide and immediate release of thiazolinedione in a multi-layer formulation.

In a preferred embodiment the pharmaceutical formulation is as follows:

(a) Lower Layer

Approximately 55 to 60% of active ingredient

Release retardant polymer A 5 – 25%

Release retardant polymer B 5 – 25%

Binding agent 2 – 10%

Diluents 0 – 10%

Non-aqueous vehicle q.s.

(b) Upper Layer

Approximately 7 – 15% of active ingredient

Diluents 50 – 70%

Disintegrants 0.2 - 0.5%

Solubilizers 0.2 – 2.0%

Colour 0.2 – 0.4%

Non-aqueous vehicle q.s.

The tablets of the invention are prepared by a method including the steps of granulation, followed by compression.

Accordingly, the present invention further provides a method for forming a tablet-form pharmaceutical composition comprising: providing a first pulverulent component comprising a first pharmaceutically active agent and a matrix material; providing a second pulverulent component comprising a second pharmaceutically active agent; and compressing the first and second pulverulent components together as discrete layers to form a tablet-form pharmaceutical composition having a first layer comprising the matrix material having the first pharmaceutically active agent dispersed therein, the dispersion of the first agent within the matrix material being effective to delay the release profile on administration of the pharmaceutical composition with respect to the release profile of the second pharmaceutically active agent provided in the composition as a second discrete layer.

More precisely, the method of preparation, which is the subject of invention comprises the steps of:

a) preparing granules of a first active substance from a pulverulent mixture of the said first active substance and one or more biodegradable inert polymeric materials, and optionally one or more additives suitable for the prolonged release of the said first active substance;

b) preparing granules of second active substance from a pulverulent mixture of the said second active substance, a disintegrating agent, a solubilising agent, optionally one or more additives such as binding agent and polymers for the preparation of the immediate release of the second active substance; and

c) combining, by compressing, in a manner known per se the two types of granules obtained in steps a) and b) above so as to obtain tablets in which the lower layer,

affording prolonged release, results from the compression of granules obtained in step a) and in which the upper layer, affording immediate release, results from the compression of the granules in step b).

The first step (a) is designed to provide granules based on the first active substance, which will lead , through compression, to the lower layer, designated as the prolonged release layer. The constituents of this layer are those of the biodegradable inert polymeric matrix defined above. The second step (b) is designed to provide granules based on a different active substance, which will lead, through compression, to the upper layer, designated the immediate release layer. Step c) leads to successive compression of the granules obtained in the preceding steps a) and b) to form a tablet.

Steps (a) and (b) involve the granulation of powder of amorphous or crystallized particles. This granulation is carried out by a wet granulation method.

The method of granulation comprises five steps;
(1)Dry mixing of its various constituents, (2) Wetting, (3) Granulation process, (4) drying and then (5) sizing.

Dry mixing consists of mixing the pulverulent excipients entering into the composition of the granules. The wetting consists in adding to the pulverulent mixture, various constituents, an aqueous solution of binder or hydroalcoholic solution of binder or alcoholic solution of binder. The granulation procedure is carried out by kneading, in a planetary or rapid type mixer granulator. The drying procedure is carried out in a fluid

bed dryer or tray dryer to achieve desired loss on drying. Sizing is done in a multimill by using suitably sized sieves to obtain the desired size distribution of the granules.

Excipients which may be used include:

Hydroxypropyl methyl cellulose:

These are well known compendial controlled release excipients capable of producing a controller swelling bio-erodible matrix, in an extended release dosage form.

Povidone USP:

This is a non-release controlling excipient. It is a water soluble granulating agent added as an aqueous or non-aqueous binder for the mixed blend of the drug and excipient.

Purified water:

It is used as a granulating fluid. Water has no environmental problems of health hazards to the workers and eliminates the necessity of solvent recovery system.

Colloidal Silicon Dioxide:

Non-releasing controlling excipient, glidant promotes granulate flow by reduction of interparticulate friction.

Isopropyl Alcohol:

It is used as a solvent for tablet coating and granulating fluid for tablet granulation. In both the process Isopropyl Alcohol is subsequently removed by evaporation.

Magnesium Stearate:

It is primarily used as a lubricant in tablet manufacture at concentration from 0.25% to 5%.

Sodium Starch Glycolate:

It is used as a disintegrant in tablet formulation. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. Usual concentration used in a formulation is between 2% to 8%.

Croscarmellose Sodium:

It is used as a disintegrant. When used in wet granulation the croscarmellose sodium is best added in both the wet and dry stages of the process so that the wicking and swelling ability of the disintegrant is best utilised.

Sodium Lauryl Sulphate:

It is used as wetting agent. It is effective in both alkaline and acidic conditions.

Description of Drawing

Figure 1 shows a bilayer tablet produced in accordance with the present invention.

Part (A) is an upper view of the tablet that has a flat beveled edge 1. Part (B) is a plan view of a tablet wherein the width 2 of the tablet which is 9mm and the length 3 of the tablet is 19mm. Part (C) is a side view of the tablet wherein the shape of the tablet is capsule shaped and the two layers are distinguished as the upper layer 4 and the lower

layer 5. "PM 30" is the embossing or engraving on the tablet as an identification and distinguishing feature and also to prevent counterfeiting.

Typical Formulations

Multilayer tablets of the invention are particularly advantageous since their method of preparation is simple, the excipient constituting them being customary. Furthermore it is possible by appropriately selecting the biodegradable inert polymeric materials to achieve accuracy in the dissolution profile to a very large extent and with precision, depending on the needs.

According to the preferred embodiment of the invention, the polymeric materials belong to the hydroxypropyl methyl cellulose group, because of the diversity properties of the polymers, it is possible to obtain modulation of the release of active ingredients.

The following examples illustrate the invention, but are not intended to limit the invention in any way

Example 1

Lower Layer

Metformin Hydrochloride	53.7% w/w
Hydroxypropyl methyl Cellulose (100,000 cps)	13% w/w
Hydroxypropylmethyl Cellulose (15,000 cps)	27% w/w

Polyvinylpyrrolidone	5.8% w/w
Magnesium Stearate	0.5% w/w

The components, except magnesium stearate, were mixed together in a blender and then granulated, using a paste containing polyvinylpyrrolidone. The granules were dried and screened to obtain a suitable particle size distribution, and mixed with hydroxypropyl methyl cellulose. When this mixture had been effectively blended, magnesium stearate was mixed with the powder.

Upper Layer

Pioglitazone Hydrochloride	13.46% w/w
Microcrystalline Cellulose	48% w/w
Starch Maize	32% w/w
Pregel Starch	2.6% w/w
Colloidal Silicon Dioxide	1.14% w/w
Sodium Starch Glycolate	2% w/w
Magnesium Stearate	0.8% w/w

The components, except magnesium stearate, colloidal silicon dioxide and sodium starch glycolate, were mixed together and granulated using a paste containing polyvinylpyrrolidone. The granules were dried and screened to obtain a suitable size distribution, and mixed with colloidal silicon dioxide and croscarmellose sodium in a blender. When this mixture had been effectively blended, magnesium stearate were mixed with the powder.

Bilayer tablets, each of 19 x 9mm dimension and each containing 500 mg of metformin hydrochloride and 15 mg of pioglitazone, were then produced in a tablet press by a two stage pressing procedure. First the lower layer (weighing 930mg) was pressed and then the ingredients for the upper layer (weighing 250g) were added to the press. Re-pressing produced a two-layer tablet weighing 1180mg.

When these tablets were tested for *in vitro* dissolution, the following results were obtained:

Time (HRS)	% Release
Upper Layer	
45 mins.	32%
2 Hrs.	43%
Lower Layer	
2 Hrs.	47-52%
4 Hrs.	62-70%
8 Hrs.	70-90%
12 Hrs.	NLT 90%

Example 2

Lower Layer

Metformin Hydrochloride	56.8%% w/w
Hydroxypropylmethyl Cellulose (100,000 cps)	15% w/w
Hydroxypropylmethyl Cellulose (15,000 cps)	23% w/w
Polyvinylpyrrolidone	4.5% w/w
Magnesium Stearate	0.6% w/w

The components, except magnesium stearate, were mixed together in a blender and then granulated, using a paste containing polyvinylpyrrolidone. The granules were dried and screened to obtain a suitable particle size distribution, and mixed with hydroxypropyl methyl cellulose. When this mixture had been effectively blended, magnesium stearate was mixed with the powder.

Upper Layer

Pioglitazone Hydrochloride	6.8% w/w
Microcrystalline Cellulose	50% w/w
Lactose	33% w/w

Polyvinylpyrrolidone	4% w/w
Sodium Lauryl Sulphate	0.8% w/w
Lake of Sunset Yellow	0.4% w/w
Croscarmellose Sodium	3% w/w
Colloidal Silicon Dioxide	1% w/w
Sodium Starch Glycolate	0.4% w/w
Magnesium Stearate	0.4% w/w

The components, except magnesium stearate and colloidal silicon dioxide, were mixed together and granulated using a paste containing polyvinylpyrrolidone. The granules were dried and screened to obtain a suitable size distribution, and mixed with colloidal silicon dioxide and croscarmellose sodium in a blender. When this mixture had been effectively blended, magnesium stearate were mixed with the powder.

Bilayer tablets, each of 19 x 9mm dimension and each containing 500 mg of metformin hydrochloride and 15 mg of pioglitazone, were then produced in a tablet press by a two stage pressing procedure. First the lower layer (weighing 880mg) was pressed and then the ingredients for the upper layer (weighing 250g) were added to the press. Re-pressing produced a two-layer tablet weighing 1130mg.

When these tablets were tested for *in vitro* dissolution, the following results were obtained:

Time (HRS)	% Release
Upper Layer	
45 mins.	90.79%
2 Hrs.	99.48%
Lower Layer	
2 Hrs.	50-60%
4 Hrs.	60-75%
8 Hrs.	70-90%
12 Hrs.	NLT 90%

Example 3

Lower Layer

Metformin Hydrochloride	55.55% w/w
Hydroxypropyl methyl Cellulose (100,000 cps)	17% w/w
Hydroxypropyl methyl Cellulose (15,000 cps)	20% w/w
Polyvinylpyrrolidone	7% w/w
Magnesium Stearate	0.45% w/w

The components, except magnesium stearate, were mixed together in a blender and then granulated, using a paste containing polyvinylpyrrolidone. The granules were dried and screened to obtain a suitable particle size distribution, and mixed with hydroxypropyl methyl cellulose. When this mixture had been effectively blended, magnesium stearate was mixed with the powder.

Upper Layer

Pioglitazone Hydrochloride	14.5% w/w
Microcrystalline Cellulose	45% w/w
Lactose	28% w/w
Polyvinylpyrrolidone	3.5% w/w
Sodium Lauryl Sulphate	2.0% w/w
Lake of Sunset Yellow	0.8% w/w
Croscarmellose Sodium	3.5% w/w
Colloidal Silicon Dioxide	1.7% w/w
Sodium Starch Glycolate	0.6% w/w
Magnesium Stearate	0.4% w/w

The components, except magnesium stearate and colloidal silicon dioxide, were mixed together and granulated using a paste containing polyvinylpyrrolidone. The granules were dried and screened to obtain a suitable size distribution, and mixed with colloidal silicon dioxide and

croscarmellose sodium in a blender. When this mixture had been effectively blended, magnesium stearate were mixed with the powder.

Bilayer tablets, each of 19 x 9mm dimension and each containing 500 mg of metformin hydrochloride and 30 mg of pioglitazone, were then produced in a tablet press by a two stage pressing procedure. First the lower layer (weighing 900mg) was pressed and then the ingredients for the upper layer (weighing 230g) were added to the press. Re-pressing produced a two-layer tablet weighing 1130mg.

When these tablets were tested for *in vitro* dissolution, the following results were obtained:

Time (HRS)	% Release
Upper Layer	
45 mins.	100.02%
2 Hrs.	100.23%
Lower Layer	
2 Hrs.	50-60%
4 Hrs.	65-80%
8 Hrs.	70-90%
12 Hrs.	NLT 90%

Example 4

Lower Layer

Metformin Hydrochloride	56.1% w/w
Hydroxypropylmethyl Cellulose (100,000 cps)	21% w/w
Carbomer 971	17% w/w
Polyvinylpyrrolidone	5.4% w/w
Magnesium Stearate	0.5% w/w

The components, except magnesium stearate, were mixed together in a blender and then granulated, using a paste containing polyvinylpyrrolidone. The granules were dried and screened

to obtain a suitable particle size distribution, and mixed with hydroxypropyl methyl cellulose. When this mixture had been effectively blended, magnesium stearate was mixed with the powder.

Upper Layer

Pioglitazone Hydrochloride	8.23% w/w
Microcrystalline Cellulose	49.0% w/w
Lactose	30% w/w
Polyvinylpyrrolidone	4% w/w
Lake of Sunset Yellow	0.2% w/w
Croscarmellose Sodium	3.5% w/w
Colloidal Silicon Dioxide	1.5% w/w
Sodium Starch Glycolate	1.0% w/w
Magnesium Stearate	0.5% w/w

The components, except magnesium stearate and colloidal silicon dioxide, were mixed together and granulated using a paste containing polyvinylpyrrolidone. The granules were dried and screened to obtain a suitable size distribution, and mixed with colloidal silicon dioxide and croscarmellose sodium in a blender. When this mixture had been effectively blended, magnesium stearate were mixed with the powder.

Bilayer tablets, each of 19 x 9mm dimension and each containing 500 mg of metformin hydrochloride and 15 mg of pioglitazone, were then produced in a tablet press by a two stage pressing procedure. First the lower layer (weighing 890mg) was pressed and then the ingredients for the upper layer (weighing 240g) were added to the press. Re-pressing produced a two-layer tablet weighing 1130mg.

When these tablets were tested for *in vitro* dissolution, the following results were obtained:

Time (HRS)	% Release
Upper Layer	
45 mins.	98.78%
2 Hrs.	99.48%

Lower Layer	
2 Hrs.	50-60%
4 Hrs.	60-75%
8 Hrs.	70-90%
12 Hrs.	NLT 90%

Example 5

Lower Layer

Metformin Hydrochloride	55.5% w/w
Hydroxypropylmethyl Cellulose (100,000 cps)	19.5% w/w
Hydroxypropylmethyl Cellulose (15,000 cps)	19.5% w/w
Polyvinylpyrrolidone	5.0% w/w
Magnesium Stearate	0.5% w/w

The components, except magnesium stearate, were mixed together in a blender and then granulated, using a paste containing polyvinylpyrrolidone. The granules were dried and screened to obtain a suitable particle size distribution, and mixed with hydroxypropyl methyl cellulose. When this mixture had been effectively blended, magnesium stearate was mixed with the powder.

Upper Layer

Pioglitazone Hydrochloride	14.6% w/w
Microcrystalline Cellulose	33% w/w
Lactose	33.0% w/w
Sodium Lauryl Sulphate	3.0% w/w
Lake of Sunset Yellow	0.4% w/w
Croscarmellose Sodium	3.5% w/w
Colloidal Silicon Dioxide	3.0% w/w
Sodium Starch Glycolate	5.5% w/w

Magnesium Stearate 1.0% w/w

The components, except magnesium stearate and colloidal silicon dioxide, were mixed together and granulated using a paste containing starch. The granules were dried and screened to obtain a suitable size distribution, and mixed with colloidal silicon dioxide and croscarmellose sodium in a blender. When this mixture had been effectively blended, magnesium stearate were mixed with the powder.

Bilayer tablets, each of 19 x 9mm dimension and each containing 500 mg of metformin hydrochloride and 30mg of pioglitazone, were then produced in a tablet press by a two stage pressing procedure. First the lower layer (weighing 900mg) was pressed and then the ingredients for the upper layer (weighing 230g) were added to the press. Re-pressing produced a two-layer tablet weighing 1130mg.

When these tablets were tested for *in vitro* dissolution, the following results were obtained:

Time (HRS)	% Release
Upper Layer	
45 mins.	100.10%
2 Hrs.	100.28%
Lower Layer	
2 Hrs.	50-60%
4 Hrs.	60-75%
8 Hrs.	70-90%
12 Hrs.	NLT 90%

CLAIMS

1. A pharmaceutical composition comprising a matrix material having first pharmaceutically active agent dispersed therein, the dispersion of the first agent within the matrix material being effective to delay the release profile of the first agent on administration of the pharmaceutical composition with respect to the release profile of a second pharmaceutically active agent provided in the composition outside of the matrix material.
2. A pharmaceutical composition according to claim 1, wherein the first pharmaceutically active agent and the second pharmaceutically active agent are each independently indicated in the treatment of diabetes.
3. A pharmaceutical composition according to claim 1 or claim 2, wherein the first pharmaceutically active agent and the second pharmaceutically active agent are selected from respectively different classes of chemical compound.
4. A pharmaceutical composition according to any one of claims 1 to 3, wherein the first pharmaceutically active agent is a biguanide compound.
5. A pharmaceutical composition according to claim 4, wherein the biguanide compound is metformin.
6. A pharmaceutical composition according to any one of claims 1 to 5, wherein the second pharmaceutically active agent is a thiazolinedione compound.
7. A pharmaceutical composition according to claim 6, wherein the thiazolinedione compound is pioglitazone.
8. A pharmaceutical composition according to any one of claims 1 to 7, wherein the matrix material is a polymeric material or mixture of polymeric materials

having the capacity to absorb water from its surrounding environment and to swell on such absorption.

9. A pharmaceutical composition according to claim 8 wherein the matrix material is selected from carbomers, cellulosic polymers, alkyl cellulosic polymers and mixtures of two or more thereof.

10. A pharmaceutical composition according to claim 9, wherein the matrix material comprises a carbomer, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxy propyl cellulose, hydroxypropyl methyl cellulose or mixtures of two or more thereof.

11. A pharmaceutical composition according to claim 10, wherein the matrix material comprises a combination of a carbomer with a cellulosic polymer.

12. A pharmaceutical composition according to any one of claims 1 to 11, wherein the first pharmaceutically active agent is dispersed substantially homogenously throughout the matrix material.

13. A pharmaceutical composition according to any one of claims 1 to 12, wherein the dispersion of the first agent within the matrix material is effective to extend the release profile of the first agent on administration of the pharmaceutical composition with respect to the release profile of a second pharmaceutically active agent.

14. A pharmaceutical composition according to any one of claims 1 to 13, provided in the form of a layered tablet, with a first layer comprising the matrix material and the first pharmaceutically active agent and a second layer comprising the second pharmaceutically active agent.

15. A pharmaceutical composition according to any one of claims 1 to 14, wherein one or both of the first and second active agents are provided in combination

with one or more pharmaceutical adjuvants selected from excipients, colourants, binders, diluents, fillers, solubilising agents, disintegrants, lubricants, glidants and taste-masking agents.

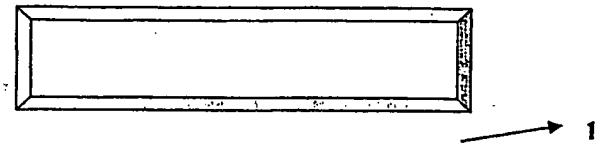
16. A pharmaceutical composition according to any one of claims 1 to 15, wherein the first and second active agents in the composition are selected to exhibit a synergistic effect for treatment of a disease or a condition.

17. A pharmaceutical composition according to any one of claims 1 to 16, wherein the second active agent is provided in combination with a solubilising agent to provide a predetermined substantially immediate release on administration of the composition.

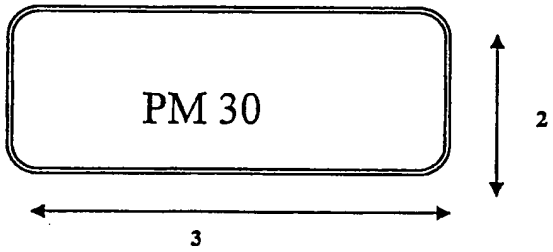
18. A method for forming a tablet-form pharmaceutical composition comprising: providing a first pulverulent component comprising a first pharmaceutically active agent and a matrix material; providing a second pulverulent component comprising a second pharmaceutically active agent; and compressing the first and second pulverulent components together as discrete layers to form a tablet-form pharmaceutical composition according to any one of claims 1 to 17

1/1

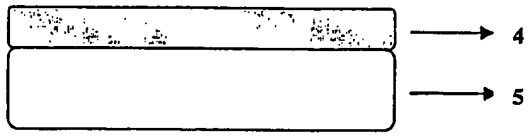
FIGURE 1



(A)



(B)



(C)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 03/00313-0

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: A61K 9/24, 31/155, 31/425, A61P 3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: A61K, A61P 3/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CAS, Medline

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/82875 A2 (AEROPHARM TECHNOLOGY, INC.) 8 November 2001 (08.11.01) *the whole document.*	1-18
X	WO 03/005991 A1 (AEROPHARM TECHNOLOGY INCORPORATED) 23 January 2003 (23.01.03) *the whole document.*	1-18

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
„L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed

„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 February 2004 (11.02.2004)	11 March 2004 (11.03.2004)
Name and mailing adress of the ISA/AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. 1/53424/535	Authorized officer MOSSER R. Telephone No. 1/53424/437

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 03/00313-0

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

In view of the large number of possible pharmaceutical compositions the search has been restricted to compositons for the treatment of diabetes.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN 03/00313-0

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO A 182875		none	
WO A 05991		none	